

Platelet Transfusion in Dengue: Peril or Protection

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Abstract

Introduction: Dengue is a common vector-borne disease in developing-countries with significant morbidity & mortality. Thrombocytopenia is being a common complication in dengue needs clear guidelines for management. Role of Platelet transfusion in this condition is bit controversial. **Method:** It was an observational, analytical case-control study based on case record review of children with Dengue with thrombocytopenia(less than 100000/cu mm) with or without minor bleeding, admitted to Cheluvamba Hospital of Mysore Medical College & Research Institute, Mysore, India throughout epidemic period of 2013(June-August). Total of 138 dengue-positive children were studied with respect to two distinct groups with objective to compare the clinical-outcome and platelet-recovery between dengue-positive children with platelet-transfusion (cases) and those without platelet-transfusion (controls). Cases and controls were analyzed for various parameters through SPSS for windows (version 20.0). P-value of < 0.05 was taken as statistically significant. **Results:** Present study included 36 cases and 102 controls whose baseline-parameters were comparable. ARDS was more common in cases than controls (p=0.000). Duration of platelet recovery, time taken to become afebrile and hospitalization were prolonged in cases as compared with the controls and were statistically highly significant (p=0.000). Another analysis in 11000 to 30000/cu mm platelet count groups revealed the similar results of prolonged duration of platelet recovery, time taken to become afebrile and duration of hospitalization amongs cases as compared with controls. **Conclusion:** There is no advantage of platelet-transfusion in dengue-positive children with thrombocytopenia with or without minor bleeds. Platelet-transfusion prolongs the duration of platelet-recovery, time taken to become afebrile and hospitalization.

Key words: dengue fever, dengue shock syndrome, dengue hemorrhagic fever, acute respiratory distress syndrome, platelet counts, platelet-transfusion.

Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease in the world and an estimated 50 million dengue infections occur annually. Case fatality rates for the South-East Asian region are 1%, but is maximum in focal outbreaks in India, Indonesia and Myanmar of 3%-5% [1].

The most dreaded complication of dengue being thrombocytopenia and bleeding with consequences. In absence of precise WHO-guidelines regarding practice of platelet-transfusion in dengue children with thrombocytopenia at various cut-off values adopted guidelines vary in many dengue endemic countries[2]. Malaysian health guidelines tells to use platelet transfusion when the count is less than 50000/cu mm if bleeding present and less than 20000/cu mm as

prophylactic use. Cut of value for platelet transfusion is 10,000/ cu mm as per Singapore clinical practical guidelines [3].

A poor health care system with underdeveloped blood transfusion facilities as in India necessitates appropriate use of blood and components especially platelets and to ensure the availability of the same for patients in whom it is really indicated & also to avoid transfusion reactions and transmissible diseases [4,5].

Objectives

Objectives of study include to compare the clinical-outcome and platelet-recovery between dengue positive children with platelet-transfusion and those without platelet-transfusion.

Methods

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Design: this study was an observational, analytical case-control study

Setting: The study was done in Pediatric department of Cheluvamba hospital, attached to Mysore Medical college and research institute, Mysore.

Patients: The study population was seropositive cases of dengue fever (NS1 and/or IgM positive) who were either dengue fever (DF), DSS or DHF admitted in Cheluvamba hospital, MMC&RI, Mysore, Karnataka, throughout the epidemic period-2013 from 1st June to 1st August.

Main Outcome Measures Studied: This study was based on case record review of children with Dengue with thrombocytopenia (less than 100000/cu mm) with or without minor bleeding, admitted to our hospital, throughout epidemic period of 2013 (June to August).

We defined total 138 patients as cases (with platelet-transfusion) and controls (without platelet-transfusion). Of these groups, age of the patient, duration of fever before admission, result of the dengue serological test, platelet count on admission and daily platelet counts, number of cases who received platelet transfusion, number of transfusions, associated reactions, resultant morbidities are documented.

Both the groups were compared and analyzed with respect to

- time taken to rise platelet count to more than 1,00,000/cu mm,
- time taken to become afebrile
- Platelet transfusion reactions
- Morbidities
- Mortality
- Duration of hospital stay

Statistical Analysis: Cases and controls were analyzed using SPSS for windows (version 20.0). P value < 0.05 was taken as statistically significant.

Results

Present study included 36 cases and 102 controls whose baseline-parameters were comparable. Mean age of cases was 8.41 years and that of controls was 8.65 years. The male to female ratio was 1.8:1 in the study.

Both the cases and controls presented with symptoms (abdominal pain, nausea, vomiting, lethargy, myalgia, headache, cough, bleeding manifestations, febrile seizure, encephalopathy) and had danger signs (hepatomegaly, splenomegaly, evidences of external and internal bleeds) which were comparable and were not concentrated to any one group ($p > 0.05$).

During follow up of the patients, we found that 6 % of the cases (2 of 36) after platelet transfusion presented with compensated shock whereas it was not evident in controls and it was statistically significant ($p=0.016$). Also, 42.1% of cases (16 of 36) after platelet transfusion had hypotensive shock whereas only 10.7% of controls (11 of 102) documented hypotensive shock and it was statistically significant ($p=0.000$).

There was presence of morbidities like pleural effusion, ascites were more evident during hospital stay in cases (55.5% and 27.77% respectively) as compared with the controls (18.62% and 9.8% respectively) and were statistically significant (p value of 0.000 and 0.008 respectively).

There were secondary dengue infections about 25% in cases and 21% in controls diagnosed based on antibody detection tests; and this value was comparable between the cases and controls ($p=0.581$).

There was evidence of more DSS and DHF in cases (38.8% and 22.2%) as compared to those in controls (22% and 8%) during hospital stay and this was statistically significant ($p=0.002$).

Fatal complication like ARDS was more common in cases (9 out of 36; 25%) as compared to controls (4 out of 102; 3.9%) and was statistically highly significant ($p=0.000$). But other complications like encephalitis, neurological deficits, hepatitis were comparable between the cases and controls ($p > 0.05$).

There were 3 deaths out of 36 cases (8.33%) and no deaths in controls mainly associated with ARDS.

Platelet recovery was much delayed in cases as compared to controls. Average duration in which platelet count raised above 1,00,000/cu mm was 15 days for cases as compared to just 9 days in controls. This observation was statistically highly significant ($p=0.000$).

The time to become afebrile was much more in cases as compared to the controls. Mean time taken to become afebrile was 6.28 days in cases as compared to just 1.57 days in controls. This observation was too statistically highly significant ($p=0.000$).

The duration of hospitalization was found to be prolonged in cases as compared to controls. Maximum number of cases 11 out of 36 (30.6%) were hospitalized for 7 days and maximum duration was 45 days in one case with complications (ARDS and ventilatory support) and mean duration of stay was 8.69 days. Maximum number of

controls 42 out of 102 (41.2%) were hospitalized for 4 days and maximum duration was 9 days and the mean

duration of stay was 4.29 days. This observation was statistically highly significant ($p=0.000$).

Table 1: Association of Thrombocytopenia with morbidities in cases and control

	Groups with respect to thrombocytopenia: cases compared with controls (p values)			Groups with respect to age: cases compared with controls (p values)		
	<10,000/cu mm	11,000-20,000 /cu mm	21,000-30,000 /cu mm	<5 year	5-10 year	10-15 year
Duration to increase platelet count to >1lakh/cu mm	0.451	0.000	0.000	0.000	0.000	0.000
Duration to become afebrile	0.171	0.000	0.000	0.000	0.000	0.001
Duration of hospitalization	0.667	0.000	0.000	0.000	0.000	0.000
ARDS	0.571	0.081	0.000	0.000	0.266	0.000

- Except in the group of lowest platelet count of <10,000/cu mm, 11,000 to 30,000/cu mm group cases had more duration to increase platelet count to >1lakh/cu mm, to be free from fever and total hospital stay. Even ARDS incidence was more in cases than controls. These findings were statistically highly significant ($p<0.05$).
- When we analyze cases and controls age wise, cases had prolonged time to increase platelet count to >1lakh/cu mm, to become afebrile and total hospital stay as compared with the controls and was statistically highly significant ($p<0.05$).
- ARDS was more common finding in cases than controls in age group of < 5years and 10-15 years ($p<0.05$), but in age group of 5-10 years, ARDS incidence was comparable ($p=0.266$).
- When we analyze cases and controls age-wise (<5years, 5-10years and 10-15years), cases had prolonged time to increase platelet count to >1lakh/cu mm, to become afebrile and total hospital stay as compared with the controls and was statistically highly significant ($p<0.05$).
- ARDS was more common finding in cases than controls in age group of < 5years and 10-15 years ($p<0.05$), but in age group of 5-10 years, ARDS incidence was comparable ($p=0.266$).

Discussion

Thrombocytopenia is a common problem in dengue, which causes a lot of concern not only to the patients but also to the relatives as well as to the attending physicians. No clear cut guidelines are available for the management of thrombocytopenia in dengue. The natural-tendency is to transfuse platelets in such patients. The thrombocytopenia in dengue is primarily immune mediated and platelet transfusion is said to worsen the thrombocytopenia by an *exalted immune response* by a strong antigenic stimulus [6]. Apart from that, the short life span of transfused platelets result only in a transient or non-sustained elevation of the platelet [6,7]. They can also induce hypersensitivity reactions and fluid-overload with complications such as pleural effusion, ascitis and pulmonary oedema.

Makroo et al recorded 15.5% and Chairulfatah et al recorded 6% of dengue cases with hemorrhagic manifestations and both observed severe bleeding with platelet count of <20,000/cu mm [8,9]. In present study, hemorrhagic manifestations were present on 22.2% cases

(petechiae, purpurae, epistaxis, hematemesis, melena) with more often associated with platelet count of <20,000/cu mm. It's known that, the bleeding in dengue may result from a combination of factors, not only the thrombocytopenia but also coagulation defect and vasculopathy[10]. Hence, minor bleeding in dengue may not be an indication for just platelet transfusion and may need coagulation profile before deciding for transfusion [11].

There was presence of morbidities like pleural effusion, ascites were more evident during hospital stay in cases (55.5% and 27.77% respectively) as compared with the controls(18.62% and 9.8% respectively) and were statistically significant. Similar findings were found in studies by Isarangkura P et.al.[12]

There was evidence of more DSS and DHF in cases (38.8% and 22.2%) as compared to those in controls (22% and 8%) during hospital stay and this was statistically significant($p=0.002$). Similar observation was found in a

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study where the incidence of bleeding increased in patients with blood transfusion as compared to those without the transfusion. Platelet transfusion has no significant effect on the incidence of bleeding which suggest that low platelet count alone may not be responsible for bleeding in DHF/DSS [10]. Another study by Charulath A et al found that in DHF/DSS, there was no difference in the frequency of bleeding observed comparing patients who received and those who did not receive platelet transfusion, suggesting that platelet transfusion did not influence the incidence of severe bleeding [9,10].

Fatal complication like ARDS was more common in cases (9 out of 36; 25%) as compared to controls (4 out of 102; 3.9%) and was statistically highly significant ($p=0.000$) which is a common expected complication associated with volume overload attributed to platelet transfusion [12] but other complications like encephalitis, neurodeficits, hepatitis were comparable between the cases and controls ($p>0.05$).

Platelet recovery was much delayed in cases as compared to controls. Average duration in which platelet count raised above 1,00,000/cu mm was 15 days for cases as compared to just 9 days in controls. This observation was statistically highly significant ($p=0.000$). It is said that timing of platelet count recovery is generally be closely associated with clinical improvement in dengue infections. It is said that platelet count recovery after hospitalization is confounded by multiple factors (such as diagnostic groups, co-infection, platelet/plasma transfusion, lowest platelet count and duration of fever at the time of hospitalization) but such observation was not found in our study [13].

The time to become afebrile was much more in cases as compared to the controls. Mean time taken to become afebrile was 6.28 days in cases as compared to just 1.57 days in controls. This observation was too statistically highly significant ($p=0.000$). Similar finding was observed in a study by Traineau R et al where they attributed the prolonged fever to the bacterial contamination of the blood components [14].

The World Health Organization (WHO) suggested clinical-improvement in the form of improved appetite, decrease in fever, absence of bleeding manifestation and platelet counts $> 50,000/\text{cu mm}$ as discharge criteria for inpatient dengue patients. With respect to this guideline, the duration of hospitalization was found to be prolonged in cases as compared to controls. Maximum number of cases 11 out of 36 (30.6%) were hospitalized for 7 days and maximum duration was 45 days in one case with

complications (ARDS and ventilatory support) and mean duration of stay was 8.69 days. Maximum number of controls 42 out of 102 (41.2%) were hospitalized for 4 days and maximum duration was 9 days and the mean duration of stay was 4.29 days. This observation was statistically highly significant ($p=0.000$).

Platelet transfusion was associated with transfusion related reactions (urticaria in 10%, fever in 18%), similar reactions were observed in a study by Sitti NR et al where they attributed the reactions to be caused by recipient antibodies reacting with white cell antigens or white fragments in the blood product or due to cytokines which accumulate in the blood products during storage [15].

Platelet transfusions are hardly ever required even with counts as low as 10,000/cumm because the circulating platelets are haematologically active and sufficient enough to prevent bleeding by thrombocytopenia per se. In general, platelet transfusions are required only when there are serious haemorrhagic manifestations [12,16,17].

According to Chuansumrit A et al transfusion requirements correlate well with the occurrence of bleeding in the gastrointestinal tract but not with the platelet count and they pointed out that mucosal bleeding may occur in any patients with dengue but, if the patients remain hemodynamically stable with fluid resuscitation/replacement, bleeding should be considered as minor [13]. As per WHO guidelines 2009, in patients with profound thrombocytopenia, strict bed rest and protection from trauma to reduce the risk of bleeding is recommended [17].

Conclusion

There is no advantage of platelet-transfusion in dengue-positive children with thrombocytopenia with or without minor bleeds. Such platelet transfusion prolongs the duration of platelet-recovery, time taken to become afebrile and hospitalization. A prospective control trial is recommended to confirm our study results.

Limitations of the study

1. One limitation of this study has the small study population & needs large multicentric study.
2. Patients given transfusion and not transfused were not of the same severity of illness at baseline.
3. There are no clear-cut guidelines in giving platelet transfusion hence, is mainly dependent on the decision of the physician which will affect the study result.

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